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Immunological studies in recurrent spontaneous abortion: effects of immunization of women with paternal mononuclear cells on lymphocytotoxic and mixed lymphocyte reaction blocking antibodies and correlation with sharing of HLA and pregnancy outcome.

Smith JB, Cowchock FS.

Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107.

The occurrence of maternal antipaternal lymphocytotoxic antibody (LCTA), mixed lymphocyte reaction blocking factors (MLRBF) and human leukocyte antigen (HLA) antigen sharing was studied in 115 couples with unexplained repeated spontaneous abortions (RSA). Comparisons were made to the same studies done on 41 couples with explained repeated miscarriages. We found no significant difference between the patient and control group with respect to the percent of couples sharing none, one, or two or more HLA-A,-B, or -DR antigens. Examination of the occurrence of LCTA and MLRBF likewise did not reveal differences between the groups, nor did the occurrence of these antibodies on initial testing correlate with HLA disparity between couples. Women with three or more spontaneous abortions were immunized with paternal mononuclear cells (MNC) if they met at least two of the following three criteria: they shared two or more HLA antigens; their serum was negative for paternal MNC-directed LCTA; their serum did not contain maternal versus paternal MLR blocking factors. Complete HLA, LCTA and MLRBF data pre- and post-treatment are available on 60 women. Sixty-three percent of women converted to LCTA positive 6 +/- 1 weeks after immunization, and 35% of women converted from negative to positive for MLR blocking after immunization. Fifty-eight women who had all three tests done prior to immunization became pregnant after immunization. Only 50% of this selected group have experienced successful pregnancy as judged by delivery of a live-born infant. In the patients presented, successful pregnancy outcome did not correlate with HLA antigen disparity, but successful patients were more likely than aborters to have either LCTA or MLRBF prior to pregnancy (28 vs. 7%). Post-immunization conversion to LCTA positive was more prevalent in the women who aborted after immunization (74%) compared to those who had successful pregnancy (48%) while MLR blocking antibody conversion from negative to positive was the same in both

groups. The data indicate that neither HLA antigen sharing nor conversion to LCTA or MLR blocking positive after paternal WBC immunization are predictors for successful pregnancy outcome. Results so far suggest that conversion to LCTA positive after immunization may have a negative influence on pregnancy outcome.

PMID: 2976829 [PubMed - indexed for MEDLINE]

1: Arch Gynecol Obstet 1990;248(2):93-101 Related Articles, Books, LinkOut

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Related Resources

Selection of patients with habitual abortion for paternal leucocyte immunization.

Carp HJ, Toder V, Gazit E, Orgad S, Mashiach S, Serr DM, Nebel L.

Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel.

After potentiation of the immune response in habitual aborters 75-85% of subsequent pregnancies are claimed to result in healthy term infants. However, all publications to date have either been based on the authors concept of the immune processes involved or an attempt to demonstrate the efficacy of treatment either empirically or by matched trials. As immunization is coming into wider clinical use, it is necessary to determine which patients will benefit from this form of treatment. This paper presents our experience with paternal leucocyte immunization over the period 1985-1988. 207 patients were classified on a clinical basis and by immunological testing. 143 patients have been immunised, 129 pregnancies have occurred in 108 patients. The vast majority of our patients have recurrent missed abortions. Only six women habitually aborted live fetuses. Two had subsequent live births. Secondary aborters seem to do well in subsequent pregnancies, whether immunized or not. The patient most likely to benefit from immunization is the Primary missed aborter who does not possess antipaternal antibody (APCA), but is induced to produce APCA by immunization. Using these criteria, 75% success rates are observed in the subsequent pregnancy. This success rate is irrespective of HLA antigen sharing or in-vitro mixed lymphocyte reactivity.

PMID: 2150303 [PubMed - indexed for MEDLINE]

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L6 ANSWER 1 OF 21 MEDLINE DUPLICATE 1
2002322241 Document Number: 22015005. PubMed ID: 12021083. Oral tolerance, systemic immunoregulation, and autoimmunity. Strobel Stephan. (Immunobiology Unit, Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, London WC1N 1EH, UK.. s.strobel@ich.ucl.ac.uk) . ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (2002 Apr) 958 47-58. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Convincing clinical and experimental evidence suggests that the disturbance of important immunoregulatory and suppressive immunological events induced after oral (mucosal) antigen exposure (oral tolerance) may lead to allergic and autoimmune diseases. Within a variety of factors, age of the host and timing of antigen (food) administration are important characteristics in the development of food allergic disease. **Induction** of **tolerance** is seen as a Th2 skewed response, which on one side may prevent harmful mucosal immune reactions but on the

other side may contribute to adverse responses in the susceptible individual. The primary mechanisms by which tolerance may be mediated include deletion, anergy, suppression, "ignorance," and apoptosis. Cell-mediated delayed hypersensitivity reactions (Th1), which are implicated in the development of autoimmune and gastrointestinal diseases, are particularly well suppressed. Regulatory events after mucosal exposure of antigen are not well characterized and remain controversial. The balance between tolerance (suppression) and sensitization (priming) is dependent on several factors, such as: (a) genetic background, (b) nature and dose of antigen, (c) frequency of administration, (d) age at first antigen exposure, (e) immunological status of the host, (f) antigen transmission via breast milk, and others. Overall there is evidence in rodents that multiple low-dose feeds are more likely to induce regulatory cytokines (e.g., **TGF-beta**, IL-10, IL-4) in part secreted by CD4+CD25+ T regulatory cells. Despite the powerful suppressive effects of oral autoantigen exposure observed in experimental models of autoimmune diseases (including bystander suppression), their translation into clinical trials of autoimmune diseases has not yet yielded the expected beneficial results.

L6 ANSWER 2 OF 21 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2

2001308456 EMBASE A role for **TGF.beta**. and B cells in immunologic tolerance after intravenous injection of soluble antigen.

Valujskikh A.; VanBuskirk A.M.; Orosz C.G.; Heeger P.S.. Dr. P.S. Heeger, Department of Immunology, Lerner Research Institute, NB30, 9500 Euclid Avenue, Cleveland, OH 44195, United States. heegerp@ccf.org.

Transplantation 72/4 (685-693) 27 Aug 2001.

Refs: 59.

ISSN: 0041-1337. CODEN: TRPLAU. Pub. Country: United States. Language: English. Summary Language: English.

AB Background. Intravenous injection of soluble antigen has been reported to induce immunologic tolerance through a variety of mechanisms including T-cell deletion, anergy, and suppression. To clarify the reported discrepancies, we studied mechanisms of intravenous tolerance to a defined transgenic minor transplantation antigen in mice. Methods. Wild-type C57BL/6 (B6) mice or congenic B6 B-cell knockout mice were made tolerant to .beta.-galactosidase (.beta.-gal). Clinical tolerance was assessed by placement of B6 .beta.-gal transgenic (tg) and third-party skin grafts. In vitro analysis of T- and B-cell immunity and in vivo treatment with anti-**TGF.beta**. antibodies were used to define mechanisms of induced tolerance. Results. Intravenous injection of .beta.-gal induced true immunologic tolerance to .beta.-gal tg skin in wild-type but not in B-cell-deficient recipients, suggesting that antigen presentation by B cells was required for the effect. The tolerogenic manipulation primed a population of CD4(+), .beta.-gal-specific, **TGF.beta** .-producing T cells. Although evidence for both anergy and suppression were observed, subsequent data demonstrated that **TGF**. **beta**. was a critical immunoregulatory mediator of the tolerant state: neutralizing anti-**TGF.beta**. antibodies fully prevented the **induction** of **tolerance** to B6 .beta.-gal tg skin grafts. Second male .beta.-gal tg grafts placed onto female recipients that were previously made tolerant to female .beta.-gal tg skin were rapidly rejected, however, suggesting that this **TGF**. **beta**.-induced tolerance could not be linked to additional antigenic determinants. Conclusions. The studies demonstrate a critical role for **TGF.beta**. in mediating tolerance after intravenous injection of antigen but additionally raise concerns about the stability of this tolerant state.

L6 ANSWER 3 OF 21 MEDLINE DUPLICATE 3

2001147668 Document Number: 20584598. PubMed ID: 11154238. Altered T-cell receptor + CD28-mediated signaling and blocked cell cycle progression in interleukin 10 and transforming growth factor-beta-treated alloreactive T

cells that do not induce graft-versus-host disease. Boussiotis V A; Chen Z M; Zeller J C; Murphy W J; Berezovskaya A; Narula S; Roncarolo M G; Blazar B R. (Department of Adult Oncology, Dana-Farber Cancer Institute, Division of Medical Oncology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.. vassiliki_boussiotis@macmailgw.dfci.harvard.edu) . BLOOD, (2001 Jan 15) 97 (2) 565-71. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The induction of anergy in T cells, although widely accepted as critical for the maintenance of tolerance, is still poorly understood at the molecular level. Recent evidence demonstrates that in addition to blockade of costimulation using monoclonal antibodies (mAbs) directed against cell surface determinants, treatment of mixed lymphocyte reaction (MLR) cultures with interleukin 10 (IL-10) and transforming growth factor-beta (**TGF-beta**) results in **induction** of **tolerance**, rendering alloreactive murine CD4(+) T cells incapable of inducing graft-versus-host disease (GVHD) after in vivo transfer to histoincompatible recipients. The present study, using these cells prior to adoptive transfer, determined that IL-10 + **TGF-beta** -tolerant CD4(+) T cells exhibit an altered pattern of T-cell receptor (TCR) + CD28-mediated signaling and are incapable of progressing out of the G(1) phase of the cell cycle during stimulation with HLA class II disparate antigen-presenting cells. TGFbeta + IL-10-tolerant cells were incapable of phosphorylating TCR-zeta, or activating ZAP-70, Ras, and MAPK, similarly to T-cell tolerized by blockade of B7/CD28 and CD40/CD40L pathways. Moreover, these cells were incapable of clonal expansion due to defective synthesis of cyclin D3 and cyclin A, and defective activation of cyclin-dependent kinase (cdk)4, cdk6, and cdk2. These cells also exhibited defective down-regulation of p27(kip1) cdk inhibitor and lack of cyclin D2-cdk4 activation, Rb hyperphosphorylation, and progression to the S phase of the cell cycle. These data link anergy-specific proximal biochemical alterations and the downstream nuclear pathways that control T-cell expansion and provide a biochemical profile of IL-10 + **TGF -beta**-tolerant alloreactive T cells that do not induce GVHD when transferred into MHC class II disparate recipients in vivo.

L6 ANSWER 4 OF 21 MEDLINE DUPLICATE 4

2001220143 Document Number: 21212138. PubMed ID: 11311114. Current and potential agents for the treatment of alopecia areata. Freyschmidt-Paul P; Hoffmann R; Levine E; Sundberg J P; Happle R; McElwee K J. (Department of Dermatology, Philipp University, Marburg, Germany.. freyschm@mailer.uni-marburg.de) . CURRENT PHARMACEUTICAL DESIGN, (2001 Feb) 7 (3) 213-30. Ref: 141. Journal code: 9602487. ISSN: 1381-6128. Pub. country: Netherlands. Language: English.

AB Alopecia areata is considered to be a T-cell mediated autoimmune disease of the hair follicle. Current immunosuppressive approaches and immunomodulatory treatment with contact sensitizers such as diphenylcyclopropenone and squaric acid dibutylester are dealt with in this review article. The efficacy of the various modes of treatment is evaluated by a review of literature and their mode of action is discussed. In accordance with the mechanism of autoimmune pathogenesis of AA, improved future treatments may be immunosuppressive or immunomodulatory, or they should otherwise protect the hair follicle from the injurious effects of the inflammation. Such possible future therapeutic approaches include the use of liposomes as an improved vehicle, application of immunosuppressive cytokines like **TGF-beta** and IL-10, inhibition of apoptosis mediated by the Fas-FasL system, inhibition of the lymphocyte homing receptor CD44v10, **induction** of **tolerance** as well as principles of gene therapy.

L6 ANSWER 5 OF 21 SCISEARCH COPYRIGHT 2002 ISI (R)

2001:952775 The Genuine Article (R) Number: 493ZB. **Induction** of **tolerance** and cross-tolerance to methacrylate contact sensitizers. Rustemeyer T (Reprint); de Groot J; von Blomberg B M E; Frosch P J;

Scheper R J. Vrije Univ Amsterdam, Univ Hosp, Dept Pathol, Amsterdam, Netherlands (Reprint); Municipal Hosp, Dept Dermatol, Dortmund, Germany. TOXICOLOGY AND APPLIED PHARMACOLOGY (1 NOV 2001) Vol. 176, No. 3, pp. 195-202. Publisher: ACADEMIC PRESS INC. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. ISSN: 0041-008X. Pub. country: Netherlands; Germany. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Induction of immunological tolerance to contact allergens might prevent undesired sensitization, in particular to occupational sensitizers, e.g., methacrylates (MA). Here, using a guinea pig model, we studied to which extent tolerance to one methacrylate might result in cross-tolerance to other congeners. Strong tolerance to the monomethacrylates hydroxy-ethyl MA (HEMA) and methyl AIA, but not to the dimethacrylate ethylene-glycol MA (EGDMA) could be induced. The induced tolerance was stable, could not be broken by repeated sensitization attempts, and was mediated by specific suppressor cells, as demonstrated in T cell transfer experiments. In HEMA-tolerized animals, strong cross-tolerance to methacrylate congeners, including EGDMA, itself being nontolerogenic and showing the lowest cross-reactivity to HEMA, was found. Thus, oral application of contact allergens, to which skin contact cannot be avoided, e.g., in occupational settings, can induce broad cross-tolerance to related substances and might offer a promising preventive approach. (C) 2001 Academic Press.

L6 ANSWER 6 OF 21 MEDLINE DUPLICATE 5

2001677042 Document Number: 21579850. PubMed ID: 11722624. Type 1 T regulatory cells. Roncarolo M G; Bacchetta R; Bordignon C; Narula S; Levings M K. (San Raffaele Telethon Institute of Gene Therapy (HSR-TIGET), San Raffaele Scientific Institute, Milan, Italy.. m.roncarolo@hsr.it) . IMMUNOLOGICAL REVIEWS, (2001 Aug) 182 68-79. Ref: 100. Journal code: 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.

AB Suppression by T regulatory (Tr) cells is essential for **induction** of **tolerance**. Many types of Tr cells have been described in a number of systems, and their biology has been the subject of intensive investigation. Although many aspects of the mechanisms by which these cells exert their effects remain to be elucidated, it is well established that Tr cells suppress immune responses via cell-to-cell interactions and/or the production of interleukin (IL)-10 and transforming growth factor (**TGF**)-**beta**. Type-1 T regulatory (Tr1) cells are defined by their ability to produce high levels of IL-10 and **TGF -beta**. Tr1 cells specific for a variety of antigens arise in vivo, but may also differentiate from naive CD4+ T cells in the presence of IL-10 in vitro. Tr1 cells have a low proliferative capacity, which can be overcome by IL-15. Tr1 cells suppress naive and memory T helper type 1 or 2 responses via production of IL-10 and **TGF-beta**. Further characterisation of Tr1 cells at the molecular level will define their mechanisms of action and clarify their relationship with other subsets of Tr cells. The use of Tr1 cells to identify novel targets for the development of new therapeutic agents, and as a cellular therapy to modulate peripheral tolerance, can be foreseen.

L6 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2002 ACS

2001:333375 Document No. 135:179549 Tolerance induction across Mls and minor histocompatibility complex by inhibiting activation of T helper type 1 in early period. Sugiura, K.; Lee, S.; Nagahama, T.; Adachi, Y.; Ishikawa, J.; Ikehara, S. (First Department of Pathology, Kansai Medical University, Osaka, Moriguchi City, 570-8506, Japan). Immunology Letters, 77(1), 25-30 (English) 2001. CODEN: IMLED6. ISSN: 0165-2478. Publisher: Elsevier Science Ireland Ltd..

AB We have previously succeeded in inducing persistent donor-specific tolerance across Mls plus multiple minor histocompatibility barriers by portal venous (p.v.) injection of donor spleen or bone marrow cells plus cyclophosphamide (CY) treatment. Microchimerism was established in the lymph-hemopoietic organs of the tolerant recipients. However, the

mechanisms, particularly the roles of CY in the tolerance induction, have not been clarified. We examd. the tolerance induction using other anti-mitotic agents and evaluated the in vitro proliferative responses and cytokine expression of T cells from the recipients after stimulation with donor alloantigens. The administration of not only CY but also mitomycin C (MMC) and cytosin arabinoside (Ara C) elicited a prolongation of skin graft survival. CY induced tolerance when it was administered 2 days after the p.v. injection, but not immediately or 4 days after the p.v. injection. T cells collected from the tolerant recipients showed no proliferative responses as a result of stimulation with donor alloantigens whereas the responses of T cells from non-tolerant recipients were significantly enhanced. Interferon-gamma (IFN.gamma.) was extensively expressed in the non-tolerant T cells from 24 to 48 h after the stimulation with donor alloantigens. In contrast, the expression of IFN.gamma. was obsd. in the tolerant T cells from 72 h after the stimulation. Also, the tolerant T cells showed the expression of interleukin-10 (IL-10) and transforming growth factor-beta 1 (**TGF -.beta.**1) from 72 h after the stimulation whereas the non-tolerant T cells did not. These data suggest that CY, when administered 2 days after the p.v. injection, induces persistent tolerance by inhibiting T helper type 1 (Th1) activity in the early period but not the Th1 activity in the later periods.

L6 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2002 ACS
2000:231598 Document No. 133:221527 **Induction** of **tolerance** in macrophages by cholera toxin B chain. Burkart, Volker; Kim, Yoong-Eun; Kauer, Manfred; Kolb, Hubert (German Diabetes Research Institute at the University of Dusseldorf, Dusseldorf, D-40225, Germany). Pathobiology, Volume Date 1999, 67(5-6), 314-317 (English) 2000. CODEN: PATHEF. ISSN: 1015-2008. Publisher: S. Karger AG.

AB Model systems of human type 1 diabetes have revealed an important role of cellular immune reactions involving macrophages and T cells in the destruction of autologous insulin-producing pancreatic .beta. cells. Recently, the cholera toxin B chain (CTB) was found to suppress T cell-dependent autoimmune diseases including autoimmune diabetes of nonobese diabetic mice. Therefore, we tested the hypothesis that CTB exerts much of its immunomodulatory activity by targeting macrophages. These studies are reviewed here. Cells of the human monocyte line Mono Mac 6 were exposed to CTB and subsequently tested for proinflammatory immunoreactivity in response to challenge with endotoxin (LPS from Escherichia coli, 10 ng/mL for 5 h). Incubation of monocytes with CTB (10 .mu.g/mL) suppressed a later proinflammatory response to LPS as demonstrated by suppression of TNF.alpha. release from 6.7.+-.0.7 ng/mL in cultures without CTB preexposure to 1.8.+-.1.1 ng/mL in CTB-pretreated cells ($p < 0.001$). In contrast, the release of IL-10 remained inducible after CTB pretreatment. RT-PCR anal. showed that the suppression of TNF.alpha. prodn. occurred at the level of mRNA formation. Control expts. excluded a role of possible contamination of CTB by endotoxin or the intact cholera toxin. Tolerance induction was maximal after 5 h of CTB exposure and persisted for 24 h. The suppressive effect of CTB was dose-dependent and no more recognizable at .ltoreq. 1 .mu.g/mL. Incubation with IL-10- and **TGF.beta.**-neutralizing antibodies during CTB pretreatment prevented tolerization of macrophages. IFN.gamma. (1,200 U/mL) was found to antagonize actions of CTB. In contrast to desensitization by low doses of LPS, tolerance induction by CTB occurred 'silently', i.e. in the absence of a measurable proinflammatory response. In view of the potent instructive role of the innate immune system on T cell responses these findings are important in understanding how CTB prevents the development of autoimmune diabetes and improves tolerance to islet autoantigens.

L6 ANSWER 9 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2000:468243 Document No.: PREV200000468243. **Induction** of

tolerance to experimental autoimmune myasthenia gravis (EAMG) by injection of dendritic cells in vitro modified with **TGF-beta** and IL-10. Yarilin, D. (1); Xiao, B.-G. (1); Yang, J.-S. (1); Link, H. (1). (1) Experimental Neurology Unit, Division of Neurology, Huddinge University Hospital, Karolinska Institute, Stockholm Sweden. Immunology Letters, (September, 2000) Vol. 73, No. 2-3, pp. 237. print. Meeting Info.: 24th European Immunology Meeting of the European Federation of Immunological Societies (EFIS) Poznan, Poland September 23-26, 2000 European Federation of Immunological Societies. ISSN: 0165-2478. Language: English. Summary Language: English.

L6 ANSWER 10 OF 21 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 6
2000232942 EMBASE Anti-TCR-specific DNA vaccination demonstrates a role for a CD8+ T cell clone in the induction of allograft tolerance by donor-specific blood transfusion. Vignes C.; Chiffoleau E.; Douillard P.; Josien R.; Peche H.; Heslan J.- M.; Usal C.; Soulillou J.-P.; Cuturi M.C.. Dr. M.C. Cuturi, Institut National de la Sante, Recherche Medicale Unite 437, Immeuble Jean Monnet, 30 boulevard Jean Monnet, 44093 Nantes Cedex 1, France. ccuturi@nantes.inserm.fr. Journal of Immunology 165/1 (96-101) 1 Jul 2000.
Refs: 41.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.
AB Donor-specific allograft tolerance can be induced in the adult rat by pregraft donor-specific blood transfusion (DST). This tolerance appeared to be mediated by regulatory cells and to the production of the suppressive cytokine **TGF-.beta.**1. A potential immunoregulatory CD8+ clone bearing a V.beta.18- D.beta.1-J.beta.2.7 TCR gene rearrangement was previously identified in DST-treated recipients. To assess the functional role of this T cell clone in the **induction** of **tolerance** by DST, we have vaccinated DST-treated recipients with a plasmid construct encoding for the V.beta.18-D.beta.1-J.beta.2.7 TCR .beta.-chain. DST- induced allograft tolerance was abolished by anti-TCR V.beta.18-D.beta.1-J.beta.2.7 DNA vaccination in six of seven recipients, whereas vaccination with the vector alone, or with the construct encoding a TCR V.beta.13 .beta.-chain, had no effect. However, the transcript number of the V.beta.18-D.beta.1-J.beta.2.7 chain was unchanged in allografts from vaccinated DST-treated rats, suggesting that this clone was not depleted by vaccination, but rather was altered in its function. Moreover, TCR V.beta.18-D.beta.1-J.beta.2.7 DNA vaccination restored the anti-donor alloantibody production, partially restore the capacity of spleen cells from tolerized recipients to proliferate in vitro against donor cells, and decreased the inhibitory effect of **TGF-.beta.**1, seen in DST-treated recipients, in spleen cells from vaccinated DST-treated ones. This study strongly suggests that this CD8+ TCR V.beta.18-D.beta.1-J.beta.2.7 T cell clone has an effective immunoregulatory function in allograft tolerance induced by DST.

L6 ANSWER 11 OF 21 MEDLINE DUPLICATE 7
1999458927 Document Number: 99458927. PubMed ID: 10528171. Normal induction of oral tolerance in the absence of a functional IL-12-dependent IFN-gamma signaling pathway. Mowat A M; Steel M; Leishman A J; Garside P. (Department of Immunology, University of Glasgow, Western Infirmary, United Kingdom.. a.m.mowat@clinmed.gla.ac.uk) . JOURNAL OF IMMUNOLOGY, (1999 Nov 1) 163 (9) 4728-36. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB There is considerable evidence that regulatory cytokines play an important role in mediating the systemic tolerance found after oral administration of protein Ags. Although most existing work has focused on cytokines such as IL-4, IL-10, and **TGF-beta**, recent evidence from TCR transgenic systems suggests that the induction of oral tolerance is accompanied by priming of Ag-specific IFN-gamma production. IFN-gamma has also been implicated as a mediator of T cell tolerance in other models in

vivo and in vitro, including that induced by aerosol administration of protein. We show here that feeding tolerogenic doses of OVA primes for IFN-gamma production in the spleen of mice with a normal T cell repertoire. However, depleting IFN-gamma at the time of feeding OVA had no effect on the **induction** of **tolerance**. In addition, tolerance was induced normally in both IFN-gamma receptor knockout (IFN-gammaR-/-) and IL-12 p40 knockout (IL-12-/-) mice. This was the case for all components of the systemic immune response and also with a variety of feeding protocols, including those believed to induce distinct regulatory mechanisms. We conclude that IL-12-dependent IFN-gamma-mediated regulation does not play an essential role in oral tolerance.

L6 ANSWER 12 OF 21 MEDLINE DUPLICATE 8

1999384078 Document Number: 99384078. PubMed ID: 10452998. Intranasal exposure to protein antigen induces immunological tolerance mediated by functionally disabled CD4+ T cells. Tsitoura D C; DeKruyff R H; Lamb J R; Umetsu D T. (Division of Immunology and Transplantation Biology, Department of Pediatrics, Stanford University, Stanford, CA 94305, USA.. daphne.tsitoura@stanford.ca) . JOURNAL OF IMMUNOLOGY, (1999 Sep 1) 163 (5) 2592-600. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB In this study we examined the immunological parameters underlying the natural immunity to inhaled nonpathogenic proteins. We addressed this question by examining the effect of intranasal exposure to OVA in both wild-type mice and mice reconstituted with OVA-TCR transgenic CD4+ T cells. Intranasal administration of OVA induced an initial phase of activation during which CD4+ T cells were capable of proliferating and producing cytokines. Although many of the OVA-specific CD4+ T cells were subsequently depleted from the lymphoid organs, a stable population of such T cells survived but remained refractory to antigenic rechallenge. The unresponsive state was not associated with immune deviation due to selective secretion of Th1- or Th2-type cytokines, and the presence of regulatory CD8+ T cells was not required. Moreover, neutralization of the immunosuppressive cytokines IL-10 and **TGF-beta** did not abrogate the **induction** of **tolerance**. Inhibition of the interaction of T cells with CD86, but not CD80, at the time of exposure to intranasal Ag prevented the development of unresponsiveness, while selective blockade of CTLA-4 had no effect. Our results suggest that intranasal exposure to Ags results in immunological tolerance mediated by functionally impaired CD4+ T cells via a costimulatory pathway that requires CD86.

L6 ANSWER 13 OF 21 MEDLINE DUPLICATE 9

1999370040 Document Number: 99370040. PubMed ID: 10438973. B7.2 (CD86) but not B7.1 (CD80) costimulation is required for the induction of low dose oral tolerance. Liu L; Kuchroo V K; Weiner H L. (Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.) JOURNAL OF IMMUNOLOGY, (1999 Aug 15) 163 (4) 2284-90. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Oral administration of Ag leads to systemic unresponsiveness (oral tolerance) to the fed Ag. Oral tolerance is mediated through active suppression by Th2 or **TGF-beta**-secreting cells or clonal anergy/deletion, depending on the Ag dose used, with low dose favoring active suppression and high dose favoring anergy/deletion. The nature of APC and inductive events leading to the generation of oral tolerance have not been well defined. To determine the role of costimulatory molecules in the induction of oral tolerance, we have tested the effect of anti-B7.1 or anti-B7.2 mAb on the **induction** of **tolerance** by both high and low dose Ag feeding regimens. Our results show that the B7.2 molecule is critical for the induction of low-dose oral tolerance. Injection of anti-B7.2 but not anti-B7.1 intact Ab or Fab fragments inhibited the oral tolerance induced by low-dose (0.5

mg) but not high-dose OVA (25 mg) feeding. In addition, anti-B7.2, but not anti-B7.1, inhibited secretion of **TGF-beta**, one of the primary cytokines that mediates low-dose oral tolerance. Finally, in the in vivo model of experimental allergic encephalomyelitis, anti-B7.2 mAb treatment abrogated protection offered against disease by low-dose myelin basic protein feeding, while anti-B7.1 had no effect. Anti B7.2 had no effect on disease suppression by high-dose oral Ag. These data demonstrate that B7.2 costimulatory molecules play an essential role in the induction of low-dose oral tolerance.

L6 ANSWER 14 OF 21 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 10
2000091562 EMBASE **Induction** of **tolerance** in macrophages by cholera toxin B chain. Burkart V.; Kim Y.-E.; Kauer M.; Kolb H.. Dr. V. Burkart, German Diabetes Research Institute, University of Dusseldorf, Auf'm Hennekamp 65, D-40225 Dusseldorf, Germany. burkart@dfi.uni-duesseldorf.de. Pathobiology 67/5-6 (314-317) 1999.
Refs: 6.
ISSN: 1015-2008. CODEN: PATHEF. Pub. Country: Switzerland. Language: English. Summary Language: English.

AB Model systems of human type 1 diabetes have revealed an important role of cellular immune reactions involving macrophages and T cells in the destruction of autologous insulin-producing pancreatic .beta. cells. Recently, the cholera toxin B chain (CTB) was found to suppress T cell-dependent autoimmune diseases including autoimmune diabetes of nonobese diabetic mice. Therefore, we tested the hypothesis that CTB exerts much of its immunomodulatory activity by targeting macrophages. These studies are reviewed here. Cells of the human monocyte line Mono Mac 6 were exposed to CTB and subsequently tested for proinflammatory immunoreactivity in response to challenge with endotoxin (LPS from Escherichia coli, 10 ng/ml for 5 h). Incubation of monocytes with CTB (10 .mu.g/ml) suppressed a later proinflammatory response to LPS as demonstrated by suppression of TNF.alpha. release from 6.7 .+-. 0.7 ng/ml in cultures without CTB preexposure to 1.8 .+-. 1.1 ng/ml in CTB-pretreated cells ($p < 0.001$). In contrast, the release of IL-10 remained inducible after CTB pretreatment. RT-PCR analysis showed that the suppression of TNF.alpha. production occurred at the level of mRNA formation. Control experiments excluded a role of possible contamination of CTB by endotoxin or the intact cholera toxin. Tolerance induction was maximal after 5 h of CTB exposure and persisted for 24 h. The suppressive effect of CTB was dose-dependent and no more recognizable at .ltoreq. 1 .mu.g/ml. Incubation with IL-10- and **TGF.beta** .-neutralizing antibodies during CTB pretreatment prevented tolerization of macrophages. IFN.gamma. (1200 U/ml) was found to antagonize actions of CTB. In contrast to desensitization by low doses of LPS, tolerance induction by CTB occurred 'silently', i.e. in the absence of a measurable proinflammatory response. In view of the potent instructive role of the innate immune system on T cell responses these findings are important in understanding how CTB prevents the development of autoimmune diabetes and improves tolerance to islet autoantigens. Copyright (C) 2000 S. Karger AG, Basel.

L6 ANSWER 15 OF 21 MEDLINE DUPLICATE 11
1998220785 Document Number: 98220785. PubMed ID: 9562316. Nasal administration of multiple antigens suppresses experimental autoimmune myasthenia gravis, encephalomyelitis and neuritis. Shi F D; Bai X F; Xiao B G; van der Meide P H; Link H. (Division of Neurology, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden.) JOURNAL OF THE NEUROLOGICAL SCIENCES, (1998 Feb 18) 155 (1) 1-12. Journal code: 0375403. ISSN: 0022-510X. Pub. country: Netherlands. Language: English.

AB Oral tolerization with acetylcholine receptor (AChR) and myelin basic protein (MBP) prior to immunization with AChR+MBP+ complete Freund's adjuvant (CFA) alleviated clinical signs of experimental autoimmune myasthenia gravis (EAMG)+experimental allergic encephalomyelitis (EAE) and

AChR- or MBP-specific T and B cell responses. Tolerance induced via the nasal route needs much less tolerogen and may still be as effective as oral tolerance induction. We now immunized Lewis rats with AChR+MBP+bovine peripheral nerve myelin (BPM)+CFA, which resulted in a multiphasic clinical picture with a combination of clinical signs of the EAMG+EAE+experimental allergic neuritis (EAN), accompanied by massive macrophage infiltrations in sections of muscle, spinal cord and sciatic nerve, and strong T and B cell responses to AChR, MBP and BPM in lymphoid organs. Nasal administration of microg doses of AChR+MBP+BPM prior to immunization with a mixture of these antigens+CFA effectively suppressed the incidence and severity of clinical disease, reduced macrophage infiltrations in sections of muscle, spinal cord and sciatic nerve, and down-regulated autoreactive T cell responses to the three antigens in lymphoid organs. Numbers of AChR-, MBP-, BPM-reactive Th1 type of cytokine interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha mRNA expression in lymph node cells were markedly suppressed, while transforming growth factor-beta (**TGF-beta**) mRNA expression was upregulated from nasally tolerized rats, suggesting an active suppression mechanism may act partly in the **induction** of **tolerance**. The results implicate the possibility to establish multiple autoantigen-based vaccination for the prevention of autoimmune diseases in humans.

L6 ANSWER 16 OF 21 MEDLINE DUPLICATE 12

1998008171 Document Number: 98008171. PubMed ID: 9344693. Mucosal tolerance: a two-edged sword to prevent and treat autoimmune diseases. Xiao B G; Link H. (Division of Neurology, Karolinska Institute, Stockholm, Sweden.) CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY, (1997 Nov) 85 (2) 119-28. Ref: 59. Journal code: 0356637. ISSN: 0090-1229. Pub. country: United States. Language: English.

AB Mucosal administration of autoantigens results in the development of a state of peripheral immunological tolerance. Depending upon the dose of antigen administered, anergy/deletion of antigen-specific T cells (higher doses) and/or selective expansion of cells producing immunosuppressive cytokines (**TGF-beta**, IL-4, and IL-10) (lower doses) are two major mechanisms in mucosal tolerance **induction**. Mucosal **tolerance** is more effective after nasal compared to oral administration of antigens at the same dose. A large series of studies have demonstrated that mucosal tolerance by oral or nasal antigen administration effectively prevents several experimental disease models (EAE, EAMG, EAN, EAU, IDDM, and CIA). Mucosal antigen administration is superior in prevention to treatment of autoimmune diseases. To broaden the effectiveness of mucosal tolerance, a conjunction of tolerogens with cytokines/CTB might enhance suppression of clinical disease. Based on experimental experience with mucosal tolerance, trials in humans are ongoing in MS, RA, and uveitis. However, mucosal tolerance induction is related to the route of antigen administration (oral, nasal, parentetal), type of antigen (whole protein, peptide, altered peptide), and timing with regard to disease onset and may represent a two-edged sword. In particular, the risks of worsening an ongoing autoimmune disease by mucosal antigen administration have been incompletely addressed. Here we give an overview on some recent developments in this field where, however, much more studies are needed to define an ultimate and safe procedure.

L6 ANSWER 17 OF 21 CAPLUS

1997:698221 Document No. 127:344993 Dendritic cells and the balance between transplant tolerance and immunity. Thomson, Angus W.; Lu, Lina; Steptoe, Raymond J.; Starzl, Thomas E. (Pittsburgh Transplantation Institute and Departments of Surgery, Molecular Genetics and Biochemistry, University of Pittsburgh, Pittburgh, PA, 15213, USA). Immune Tolerance, International Symposium on Immune Tolerance, Annecy, Fr., May 9-11, 1996, 173-185. Editor(s): Banchereau, Jacques. Elsevier: Paris, Fr. (English) 1996. CODEN: 65FCA6.

AB A review and discussion with 70 refs. describing the immunobiol. of dendritic cells (DC) in relation to organ transplantation with special emphasis on the conditions that may det. their tolerogenicity. The DC whose allostimulatory function is impeded either by incomplete phenotypic maturation, selective blockage of costimulatory mols. (i.e., using CTLA-4-Ig) or the influence of specific cytokine-gene products (i.e., IL-10, **TGF.beta.**) exhibit activity consistent with the **induction** of **tolerance** than than an immunogenic DC function. In addn., the expression by DC of key mols. assocd. with inhibition of T cell growth or induction of T cell apoptosis (i.e., NO, FasL) suggests that these important APC have potential to impose restraint on immune reactivity.

L6 ANSWER 18 OF 21 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

96152211 EMBASE Document No.: 1996152211. Inactivation of Th1 and Th2 cells by feeding ovalbumin. Mowat McI. A.; Steel M.; Worthey E.A.; Kewin P.J.; Garside P.. Department of Immunology, University of Glasgow, Western Infirmary,Glasgow G11 6NT, United Kingdom. Annals of the New York Academy of Sciences 778/- (122-132) 1996.
ISSN: 0077-8923. CODEN: ANYAA. Pub. Country: United States. Language: English. Summary Language: English.

AB Several different mechanisms have been implicated in oral tolerance to protein antigens, depending on the nature and dose of antigen used and the species under study. Here, we have investigated the basis of unresponsiveness in a well-established model of oral tolerance in mice fed 25 mg ovalbumin (OVA). Our results show that CD8+ T-cell activity is suppressed by feeding OVA and that these cells are not required for the **induction** of **tolerance**. CD4+ T cells are essential for tolerance to occur, but both Th1 and Th2 cell-dependent functions are tolerized equally in OVA-fed mice. Peripheral lymph node cells from tolerized mice rapidly undergo apoptosis when cultured in vitro but produce substantial amounts of transforming growth factor .beta. (**TGF.beta.**) in response to OVA. The appearance of tolerance in vivo is preceded by a transient phase of T-cell priming, and we propose that this model of oral tolerance reflects partial activation of T cells by fed antigen, leading to selective production of **TGF .beta.** and consequent inactivation of all effector T cells. These findings indicate that the active suppression and clonal anergy identified previously in mice with oral tolerance may not be mutually exclusive phenomena.

L6 ANSWER 19 OF 21 MEDLINE

97305439 Document Number: 97305439. PubMed ID: 9161697. Induction of immunotolerance in rats by intratesticular administration of an eicosapeptide of bovine S-antigen. Ren J; Singh A K; Gregerson D S; Shichi H. (Department of Ophthalmology, Wayne State University, Detroit, MI, USA.) AUTOIMMUNITY, (1996) 25 (1) 19-31. Journal code: 8900070. ISSN: 0891-6934. Pub. country: Switzerland. Language: English.

AB Immunization of albino LEW rats with a retinal soluble antigen (S-antigen) induces experimental autoimmune uveoretinitis (EAU) which shows clinical features resembling those of human uveitis. Several uveitogenic epitopes have been identified in the antigen. This study reports that an intratesticular injection of low doses of a uveitogenic eicosapeptide (P343-362) of S-antigen prior to immunization with the same peptide prevented the onset of EAU by inducing systemic tolerance, designated orchidic tolerance. Splenic lymphocytes of both CD4+ and CD8+ subsets from tolerized rats transferred orchidic tolerance to syngeneic recipients and protected them from subsequent EAU **induction**. Orchidic **tolerance** elicited by low antigen dosage was mediated, in part, by active suppression due to suppressor or regulatory cells. At high antigen doses, however, regulatory activity was reduced possibly due to the induction of anergy in regulatory cells, and EAU severity increased. The CD4+ regulatory T cells from tolerized rats showed enhanced expression of

IL-4 mRNA compared with CD4+ cells from control rats. Increased immunoreactivity for IL-4, IL-10 and **TGF-beta** was observed in the spleen and lymph nodes of tolerized animals. The results suggest that orchidic tolerance induced by low doses of P343-362 is mediated in part by CD4+ regulatory cells secreting Th2 cytokines.

L6 ANSWER 20 OF 21 MEDLINE DUPLICATE 13

95180840 Document Number: 95180840. PubMed ID: 7875676. Spontaneous acceptance of rat liver allografts is associated with an early downregulation of intragraft interleukin-4 messenger RNA expression. Farges O; Morris P J; Dallman M J. (Nuffield Department of Surgery, John Radcliffe Hospital, University of Oxford, United Kingdom.) HEPATOLOGY, (1995 Mar) 21 (3) 767-75. Journal code: 8302946. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB Liver allografts are not rejected in the fully incompatible Lewis-RT1(1) (LEW) to blood group D Agouti-RT1a (DA) rat strain combination despite an early infiltration by recipient mononucleated cells that initially display a phenotype, an ability to respond to interleukin-2 (IL-2) and donor-specific cytotoxicity indistinguishable from that observed in the rejected, DA to LEW combination. To further analyze the mechanism of this tolerance, we have compared in these two combinations, as well as in syngeneic grafts and in normal livers, the presence of intrahepatic cytokine transcripts (IL-1 alpha, IL-2, IL-4, IL-6, IL-10, tumor necrosis factor [TNF]-alpha, TNF-beta, and transforming growth factor [**TGF**]-**beta**) by a semiquantitative polymerase chain reaction (PCR) or by northern-blotting. In normal livers or syngeneic grafts, IL-1 alpha, TNF-beta, and **TGF-beta** were the only cytokines detected by these methods. The levels of all cytokine transcripts were increased in allogeneic grafts. Expression of cytokine transcripts was very similar in the two allogeneic strain combinations except IL-4, which was expressed at a much lower level in the nonrejected strain than in the rejected strain from day 2 onward. We conclude that selective downregulation of IL-4 gene expression is associated with, and a potential mediator of, the **induction** of **tolerance** in this model.

L6 ANSWER 21 OF 21 MEDLINE DUPLICATE 14

94196895 Document Number: 94196895. PubMed ID: 8147131. [Present and future therapeutic strategies in rheumatoid arthritis]. Gegenwartige und zukunftige Therapiestrategien der rheumatoiden Arthritis (RA). Schacht E. (E. Tosse & Co. GmbH, Hamburg.) ZEITSCHRIFT FUR RHEUMATOLOGIE, (1993 Nov-Dec) 52 (6) 365-82. Ref: 197. Journal code: 0414162. ISSN: 0340-1855. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

AB The triad of inflammation, immunoproliferation and synovial hyperplasia is recognized in the pathogenesis of rheumatoid arthritis, however, the sequence of events remains as highly controversial as ever. The "RA pyramid" was established on the assumption that inflammation is at the top with the destructive processes as sequelae. The moderate successes achieved by conservative therapy with regard to long-term outcome cast doubt on this hypothesis. Inhibitors of prostaglandin synthesis have not been and are not disease modifying. Do substances which influence the endothelial adhesion molecules or leucocyte adhesion receptors (leumedines) promise to be more successful? Do the empirically developed disease modifying antirheumatic drugs (Gold parenteral, MTX) have to be administered earlier? Unfortunately, there is a need for a differential diagnosis which is prognostically valid with regard to the dynamics and aggressiveness of rheumatoid arthritis. Moreover, a pharmacological basis for optimally founded combination strategies is also lacking. Presently, the emphasis of research is directed at the regulation of dysfunctional immune systems. Immunosuppressives (cyclosporin A), cytokine antagonists, receptor antagonists and soluble cytokine receptors (IL-1, IL-6, TNF-alpha), antibodies against lymphocyte subgroups (CD4, CD7) or against cytokines and their receptors are part of the arsenal for the medium term. Too little is still known about the role of protective cytokines (

TGF-beta, IL-4, gamma-INF). Currently, however, it is prognosticated that these targeted therapies will only succeed in RA subgroups or only in intelligent combinations. More attractive alternative are strategic therapy modalities which intervene very early in the pathological process, such as the modulation of antigen presentation (MHC blocking peptides, T-cell receptor antagonists, T-cell vaccination) or the **induction** of **tolerance** against autoantigens through the oral administration of antigens (collagen II, HSP's, OM-8980). If the center of the pathological process, however, is found in the synovial proliferation of tumor-like cell clusters, then there are only a few years at the beginning of the disease when there is a real chance to impede destruction. In this case, aggressive induction therapy can be the only key to success. In the future, specifically active cytostatics (inhibitors of angiogenesis) will have to be developed and clinical trials conducted on adjuvant therapies with substances which strengthen bone and cartilage, making them more resistant to aggressive cell clusters (bisphosphonates, calcitonins, metalloproteinase- or collagenase-inhibitors).

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Suppression of natural killer cell activity by monocytes following immunotherapy for recurrent spontaneous aborters.

Higuchi K, Aoki K, Kimbara T, Hosoi N, Yamamoto T, Okada H.

Department of Molecular Biology, Nagoya City University Medical School, Japan.

PROBLEM: Natural killer (NK) cell activity has previously been shown to decrease in normal pregnancy as compared with the nonpregnancy state. The purpose of this study was to determine NK cell activity in recurrent aborters and to investigate the kinetics of NK cell activity following immunotherapy. METHODS: Recurrent aborters (N = 17) were immunized with husbands' mononuclear cells (1 x 10(8)) twice during the early stage of current pregnancy. NK cell activity of recurrent aborters as well as that of normal pregnant (N = 12) and nonpregnant (N = 6) women (controls) was determined by 51Cr release assay. Monocytes were depleted from the mononuclear cell fraction and its effect on the NK cell activity was determined as well. RESULTS: At around 5 wk of gestation, NK cell activity in recurrent aborters before treatment was significantly higher (28.0 +/- 5.1%) than that in normal pregnancy (18.9 +/- 4.3%) ($P < 0.01$). Following immunotherapy, NK cell activity of recurrent aborters (N = 13) who maintained their pregnancy decreased significantly (21.7 +/- 8.9%) ($P < 0.05$). In contrast, NK cell activity of recurrent aborters (N = 4) who aborted their current pregnancy did not decrease. Depletion of monocytes resulted in a significant increase in NK cell activity ($P < 0.05$). CONCLUSIONS: This study suggests that the immunotherapy induces suppression of NK cell activity which may contribute for the maintenance of pregnancy. Moreover, monocytes may be involved in this suppression.

PMID: 7546238 [PubMed - indexed for MEDLINE]

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Maternal immunization by husband's leukocytes for repeated fetal death associated with mild pre-eclampsia--case report with successful outcome.

Steck T, Westphal E, Wurfel W.

Department of Obstetrics and Gynecology, University of Wurzburg, Federal Republic of Germany.

We report a case of repeated fetal death at 31 gestational weeks associated with mild non-proteinuric pre-eclampsia and intrauterine growth retardation. After double intradermal immunisation with paternal leukocytes, a third pregnancy proceeded uneventfully until it ended at 38 weeks. Maternal anti-paternal blocking antibody activity was assessed by the erythrocyte antibody inhibition (EAI) test. Serologic testing revealed that the couple did not share HLA class I antigens. The mechanisms underlying the likely benefit from immunotherapy are discussed.

PMID: 1471910 [PubMed - indexed for MEDLINE]

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Treatment of recurrent spontaneous abortion by immunization with paternal lymphocytes: correlates with outcome.

Gatenby PA, Moore H, Cameron K, Doran TJ, Adelstein S.

Clinical Immunology Centre, Royal Prince Alfred Hospital, New South Wales, Australia.

Previous observations have suggested that defective recognition of fetal alloantigens by the maternal immune system is associated with recurrent pregnancy failure and that this may be prevented by boosting the maternal immune system with paternal or pooled third-party leukocytes. The mechanism whereby this process achieves success is not clear, and accordingly to explore this we immunized 28 couples with recurrent fetal loss with 80 x 10(6) paternal peripheral blood mononuclear leukocytes (PBML) and followed various immunological parameters. The couples studied, in whom 55% achieved a successful pregnancy, showed no increase in sharing of human lymphocyte antigen (HLA)-A, -B, or -DR antigens and no consistent evidence of a decreased mixed leukocyte reaction (MLR) or MLR plasma-blocking factors compared with control couples. Immunization did not alter these parameters but did induce antipaternal lymphocytotoxins, although the presence of the latter did not correlate with pregnancy outcome. There was a correlation between rapid conception after immunization and a subsequent successful pregnancy. A successful pregnancy also correlated with sustained postimmunization, postconception maternal antipaternal allospecific CD-8+ suppressor T cells. Although these findings provide overall evidence that immunization produces changes in the way in which the maternal immune system interacts with the fetus, larger numbers of couples and a higher dose of paternal lymphocytes will be needed to establish clearly whether this therapy works and its mechanism of action.

PMID: 2765130 [PubMed - indexed for MEDLINE]

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